

of El-Rashidy, Lowrey and Reilly, all references previously cited and for the same reasons as in the Office Action mailed May 23, 2001. Claims 43-47 were rejected under 35 U.S.C. 103(a) as unpatentable over Nahoum. Additionally, claims 32-33 were rejected under 35 USC § 112 first paragraph and claims 32-33, 38 and 43 were rejected under 35 U.S.C. § 112 second paragraph. Applicant traverses these rejections and requests reconsideration of the claims in view of the amendments, the following remarks and attached submissions.

### **Obviousness under § 103(a)**

Applicant claims methods and compositions for treating sexual dysfunction in a female subject in need of such treatment, comprising providing a vasoactive formulation having an effective dose of a vasoactive agent selected from misoprostol and misoprostol acid and topically administering the formulation to the clitoris or vagina of the subject for treating sexual dysfunction. This claim springs out of Applicants' surprising discovery that, unlike alprostadil (PGE<sub>1</sub>), misoprostol functions surprisingly well as a vasoactive agent (H<sub>3</sub> agonist combinations à la Nahoum need not apply). Misoprostol is particularly well-suited for use in non-organic vehicles to be administered transdermally to the exceptionally sensitive dermal tissue of the female genitalia without irritation. Moreover, because of structural chemical differences which distinguish misoprostol from alprostadil (PGE<sub>1</sub>), misoprostol can be delivered more efficiently in certain preferred vehicles, far better than has heretofore been known, and that delivery vehicle-primary vasoactive agent combination is specifically better suited for working across the dermal layers which are located at the female genitalia than alprostadil or other PGE<sub>1</sub> analogues; better in terms of efficacy, reduced target tissue irritation associated with known carrier vehicles, and active ingredient permeation into the target tissues. These same structural differences may be responsible for making misoprostol much more soluble in water and therefore more amenable to being used in aqueous carriers, a highly prized property in many pharmaceutical endeavors, and especially those where mucosal contact is contemplated.

Claims 27-42 are rejected under 35 U.S.C. § 103 in view of Nahoum and Buyuktimkin in view of El-Rashidy, Lowrey and Reilly. Nahoum is concerned with using H<sub>3</sub> agonists as a primary active ingredient for treating sexual dysfunction of men and women. In contrast with Nahoum, Applicant does not claim using misoprostol as an adjunct for H<sub>3</sub> agonist therapy (Nahoum

specifically refers to “second therapeutically active compounds”, Col. 9, line 52, defined in a relatively non-specific manner as “facilitators, potentiating agents and/or as erectogenic agents” Col. 9, line 64-65).

Nahoum proceeds in Col. 10, line 1 et seq. to equate as examples of “second therapeutically active compounds” such seemingly unrelated compounds as alprostadil, histamine, calcitonin gene related peptides or vasoactive intestinal peptide, nifedipine, verapamil, diltiazem,  $\alpha$ -adrenergic receptor blockers, haloperidol, indomethacin, papaverine, etc. Since no distinction is made between any of these compounds as second therapeutically active compounds, one asks one’s self, “How would one of skill in the art know, from reading Nahoum, to select misoprostol from all of these possibilities, as a dermal penetrating, vasoactive agent which is particularly well-suited for use in non-organic vehicles to be administered transdermally to the exceptionally sensitive dermal tissue of the female genitalia without irritation?” The answer, of course, is that one cannot learn that from Nahoum, or the other cited references. There is simply no motivation from Nahoum, or any of the other cited references, to select misoprostol as being better suited for the claimed invention than those recited in Nahoum’s pharmacopaeic litany. Had Nahoum actually tried misoprostol in a topical administration, either alone or with  $H_3$  agonists, the results would have been so startling that he would not have repeatedly referred to intraurethral administration of  $PGE_1$  in combination with  $H_3$  agonists (Col. 19, lines 7 et seq.). Instead, Nahoum merely equates misoprostol with  $PGE_1$  and papaverine as equal, though ambiguously defined, alternatives for use as vasoactive paracrine mediators (Nahoum, Col. 9, line 66) because he failed to appreciate misoprostol’s special qualities in the arena of concern.

Thus, the Examiner is mistaken in asserting that misoprostol and alprostadil are synonomous and thus interchangeable in the art. Applicant asserts that misoprostol has heretofore been unrecognized as being far better than previously known. Moreover, because of structural differences which distinguish misoprostol from alprostadil ( $PGE_1$ ), misoprostol can be delivered more efficiently in certain preferred vehicles, far better than has heretofore been known, and that delivery vehicle-primary vasoactive agent combination is specifically better across the dermal layers which are located at the female genitalia than alprostadil or other  $PGE_1$  analogues; better

in terms of effectiveness, reduced target tissue irritation associated with known carrier vehicles, and active ingredient permeation into the target tissues.

As evidence of the unobviousness of the claimed invention, Applicant submits herewith, accompanied by a further Declaration by Mr. Fotinos, dramatic data which shows that in trials comparing topical administration of PGE<sub>1</sub>, misoprostol and a placebo, 71% of female subjects using misoprostol had a positive therapeutic effect, some with dramatic results, whereas only 7% of those treated with PGE<sub>1</sub> showed any effect, and that result is the same as treatment by the placebo.

Since no reference has been cited which shows or teaches the use of misoprostol as a primary vasoactive agent for treatment of female sexual dysfunction by topical administration to the clitoris or vaginal area, and no reference cited suggests how particularly well-suited misoprostol is for such an application, Applicant does hereby submit that the rejection of claims 27-47 under 35 U.S.C. §103(a), either in view of Nahoum alone or in combination with any of the cited prior art, should be reconsidered and withdrawn and the claims should be allowed.

The Examiner has asserted, in rejecting claims 29-30 that Nahoum discloses the use of both alprostadil and misoprostol for treating sexual dysfunction. However, the Examiner fails to appreciate that Nahoum equates the compounds and uses them as alternatives to one another. Nahoum does not combine alprostadil with misoprostol, nor does he suggest any reason why one would use both misoprostol and alprostadil together. Nahoum does not recognize that mixing the two compounds can result in a synergistic effect, one result of which is better delivery of alprostadil than that achieved using alprostadil on its own. Additionally, Nahoum could not appreciate, much less obviate, the subject matter of claim 31 of combining misoprostol with a second vasodilatory agent, since for Nahoum, misoprostol was merely mentioned as a secondary vasoactive agent, and not truly the primary active ingredient.

#### **Rejections under 35 U.S.C. §112**

Claims 32-33 have been rejected under 35 USC § 112 first paragraph as not enabled by the specification and claims 32-33, 34 and 38 under § 112 second paragraph as being indefinite.

Applicant traverses the rejections and requests the reconsideration and withdrawal of the rejections.

Claims 32-33 relate to the administration of a topical composition primary vasoactive agents misoprostol and its free acid form and to the enhancing of various properties of such a composition by the addition of a “beneficial agent”. Beneficial effects are described in the specification at page 6, lines 15 et seq. as including moisturizing agents such as propylene glycol and glycerol for reducing treatment onset time and for increasing a result’s intensity. Other beneficial effects include reducing side effects from giving large doses of misoprostol in a single dose. Although cyclodextrin is the only specifically disclosed example of a compound which can reduce the effects of large dose administration, it would be clear to one of skill in the art from reading the specification at page 6, lines 20-25 that side effects which one would seek to reduce include shuddering, feelings of hardship (discomfort), excitement and diarrhea. It is known in the art that some of these are effects which might be reduced by the kinds of excipients used in controlled-release formulations, for example. Additionally, prior art references such as El-Rashidy are examples of the category of drugs like  $\alpha$ -cyclodextrin which one of skill in the art would consider useful for enhancing the comfort level of patients using a topical misoprostol formulation according to the present invention. Knowledge of these and other potentiating agents is widely ascribed to those skilled in the art and limiting the claims to the single example shown would unreasonably diminish the scope of the invention which merely claims topical administrations of misoprostol, misoprostol acid and known potentiating, effect-enhancing, side-effect-reducing agents and strategies which could be used therewith.

The remarks above with respect to claims 32-33 are applicable as well to the rejection under 35 USC §112 second paragraph, and are incorporated herein. With respect to claim 32 claiming an ill-defined “agent”, Applicant suggests that the term be understood as being an “agent having at least one beneficial effect” with the words “having at least one beneficial effect” being interpreted as indicated hereinabove with reference to the specification at page 6, lines 15 et seq.

The rejection of claim 38 is rendered inapplicable in view of the amendment thereto and that claim is now believed to be in allowable condition, which allowance is hereby requested.

The rejection of claim 43 is traversed in that one of skill in the art would know from reading the claim and the specification how to determine, by using the specification as a guide and by conducting a simple dose-response study, whether a beneficial effect has been achieved by a particular dose in a woman suffering from sexual dysfunction as a result of the treatment claimed herein. Applicant cannot and should not be forced to specify a specific result or level of result since the degree to which a particular patient is affected, and the cause of the disability, will often provide the baseline for determining beneficial effect. Moreover, the extent to which each individual patient can be helped by any therapy cannot be predicted, but will be evident to a skilled clinician or to the patients themselves. Specifying a particular minimum claimed dose at this juncture will unnecessarily limit the Applicants' rights to exclude all use of misoprostol as the primary vasoactive ingredient in a topical formulation for treating sexual dysfunction.

### **Other Matters**

Applicant has become aware of additional references which are submitted herewith in a Supplemental Information Disclosure Statement. Applicant's submission of these references is merely part of Applicant's sincere effort to comply in all respects with the spirit as well as the letter of Rule 56 and does not in any way imply that the references are any more relevant to the application than the references already of record.

### **Conclusion**

In view of the foregoing comments, submissions and amendments, it is believed that the application has been put into condition for allowance and early notice to that effect is respectfully solicited. The Examiner is respectfully urged to reconsider the rejections, withdraw them and allow the application with claims 27-47. If the Examiner believes that further issues remain outstanding, she is respectfully requested to contact Applicant's representative by telephone to see if the issues can be resolved telephonically or in person. Please charge any additional fee required for the timely consideration of this application to Deposit Account No.

19-4972.

Respectfully submitted,



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AMENDED CLAIMS MARKED TO SHOW REVISIONS

--30 (Amended). A method according to claim 29, wherein the second agent is alprostadil [alpostadril].--

--38 (Amended). A method according to claim 37, wherein the gel contains a polymer having a concentration of less than 4% [to form a low viscosity gel].--

--45 (Amended). A pharmaceutical composition according to claim 44, wherein the second agent is alprostadil [alpostradil].--